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CONVENTION APPLICATION FOR A PATENT

(a) Insert full name(s) of applicant(s).

I/We (a) SCHERING AKTIENGESELLSCHAFT

(b) Insert address(es) of applicant(s).

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I hereby apply for the grant of a Patent for an invention entitled

(c) Insert title of invention.

(c) INTRA-UTERINE CONTRACEPTIVE DEVICE

which is described in the accompanying complete specification. This application is a convention application and is based on the application or applications for a patent or patents or similar protection made in the following country or countries on the following date or dates:

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in (d) Germany on (e) 6.12.73 No. (f) P 23 61 206.8

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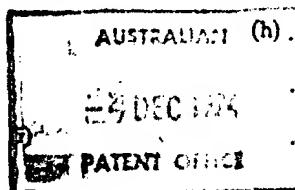
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COMMONWEALTH OF AUSTRALIA
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COMPLETE SPECIFICATION
(ORIGINAL)

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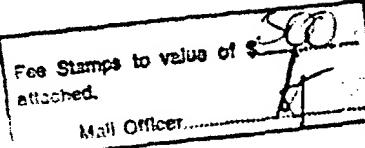
Related Art:



TO BE COMPLETED BY APPLICANT

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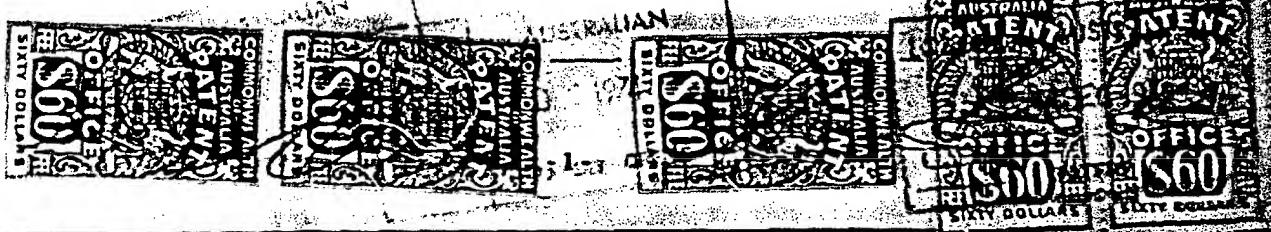


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2000

Complete Specification for the invention entitled
"INTRAM-UTERINE CONTRACEPTIVE DEVICE"

The following statement is a full description of this invention, including the best method of performing it known to me:-



The invention is concerned with a medicament-containing intra-uterine contraceptive for human use.

Medicament-containing contraceptives for intra-uterine use have been proposed in an attempt to provide contraceptives which, without preventing ovulation, are reliable in action with smaller quantities of medicaments than are required when the same medicaments are administered via the gastro-intestinal tract. The human organism can then be subjected to a reduced quantity of medicinal material with the result that side effects should be reduced or eliminated.

It has been proposed for a long time to introduce into the uterus for preventing conception devices formed of a very wide variety of materials, having a variety of shapes and being designed to act in a variety of different ways. However, the mechanism of action of these previously proposed contraceptives for intra-uterinal use has not been definitively clarified.

A device capable of intra-uterinal use for preventing conception was developed in 1920 by GRAFENBERG. The device was made of a wire material consisting of an alloy of copper and silver.

Later on various synthetic plastics materials, such as nylon, polyethylene and polyethylene/vinyl acetate, alone or with the addition of barium sulphate, were used to form a very wide variety of contraceptives for intra-uterinal use, but they were very cumbersome and bulky for the uterine cavity. Examples of such devices are the MARGULIS Spiral (U.S. Patent 3,200,815; Federal German Patents 1,416,942 and 1,441,359), BIRNBERG's Bow (U.S. Patent 3,253,590), Saf-T-Coil (U.S. Patents 3,234,938 and 3,374,788) and LIPPES LOOP (U.S. Patent 3,250,271).

With the development of T-shaped contraceptives (U.S. Patent 3,533,406), DALKON-Shield (German Offenlegungsschrift 1,956,701) and LIPPES LOOP D there became known contraceptives for intra-uterinal use made from synthetic plastics material and smaller in linear dimension and volume than previously proposed devices. The reliability in action of these contraceptives was increased by applying metallic copper to the surface of the device (compare Zipper, Amer.J.Obst.Gynec. 105, 1274-1278 (1969) and Jecht et al., Contraception, 7(5), 381 (1973)) or by the incorporation of medicaments in the synthetic plastics material. There were dispersed as medicaments in the synthetic plastics material copper powder or steroid hormones having a gestagenic action. One construction of the DALKON Shield, for example, contained copper highly dispersed in the synthetic plastics carrier. The COPPER-T and COPPER-7 (U.S. Patent 3,563,235) were partially bound round with copper wire, and the COPPER TCu 220 C (U.S. Patent 3,533,406) was partially covered with copper sleeves (U.S. Patent 3,563,235). The reliability in contraceptive action of the devices for intra-uterinal administration provided on the surface with copper was increased by the additional application of zinc or silver [see U.S. Patent 3,563,235; Zipper et al., Amer.J.Obst.Gynec. 105, 1529-534 (1969a); Zipper et al., Human fertility control through the use of endouterine metal antagonism of trace elements in control of human fertility, Nocel 15, Almquist & Wiksell, Stockholm 1971, pp. 199].

There have also been proposed intra-uterine contraceptives consisting of a device formed of a synthetic plastics material and having connected thereto a capsule of silicone rubber containing medicament. Such combination-contraceptives are also intended for

application in the cavum uteri (Int.J.Fert. 15 (1970) 210).

It has been found, however, that previously proposed contraceptives containing medicaments for intra-uterinal use, and also similarly shaped devices free from medicament, lead during the period of use to undesired side effects such as haemorrhages and pains [FORTIER et al., J.Amer.Obstet.Gynec. 115 (1973)291; TATUM, Contraception 5 (1972)179; MISHELL et al., Amer.J.Obstet.Gynec. 116 (1973) 1092].

Disadvantages of previously proposed contraceptives for intra-uterinal use are a risk that spontaneous expulsion will occur, a need to remove the contraceptive on medical grounds and the occurrence of pregnancies. A need to remove the contraceptive especially on account of side effects tends to occur at the beginning of the period of use [AVERY, Rep.Popul.Family Plan 4,6: (1973)139].

The most frequent side effects of known contraceptives for intra-uterinal use are haemorrhages and pains. The number of removals of intra-uterinally applied contraceptives necessitated by occurrence of these troubles is greater for the bulky devices formed of synthetic plastics than for the lessbulky devices such as the DALKON-Shield, T-shaped contraceptives or LIPPES LOOP D.

Side effects and removals necessitated by side effects and also expulsions of the intra-uterine contraceptives made of synthetic plastics material do not, however, result solely from the unfavourable shape and dimensions of these devices. Further important factors in this connection are the elasticity and hardness of the synthetic plastics material. Devices made of synthetic plastics material of too low an elasticity and of high hardness cause frequent pains and spasms. These devices must be made in different sizes to

correspond to the dimensions of the cavum uteri. Contraceptives made of synthetic plastics material that is too soft may twist within the uterus and are then often spontaneously expelled.

5 Occasionally, they penetrate the uterine musculature. Fragments of such intra-uterinally used contraceptives and intact devices, if these have penetrated the wall of the uterus, enter the peritoneal cavity and there lead to further injuries or ligature the intestinal convolutions.

Statistical studies have shown that, with the less bulky
10 intra-uterine contraceptives made of synthetic plastics material the frequency of side effects and spontaneous expulsions is lower than for bulky contraceptive devices. The absolute number of undesired side effects and spontaneous expulsions, however, is too high to be tolerable for either type of intra-uterine contraceptive device. Also, in the case of the less bulky intra-uterine contraceptives there have been observed side effects such as the occurrence of dysmenorrhoea, metromenorrhagia and leucorrhoea associated with continuous pain and occasionally convulsive pain [compare, for example, Ostergard et al., *Contraception* 4(5), 313-317 (1971);
15 Portruff et al., *Am.J.Obst.Gynec.* 114(7). 934-937 (1972); Taylor et al. *Obst.Gynec.* 41(3), 404-413 (1973); Bucmann, *Fert. Steril.* 21(4), 348-355 (1970)]. The pregnancy rate calculated by the life-table method [Tietze, *Intra-Uterine Contraception, Recommended Procedures for Data Analysis Studies in Family Planning*, No. 18 (Suppl.), The Population Council, New York, 1967] when these contraceptives are used is such as to cast doubt on their reliability [Fuchs et al., *Contraception* 5(2), 119-127 (1972), Baeyertz, *Austr.N.Z.J. Obst.*

Gynec. 11, 117-121 (1971); Davis, Amer.J.Obst.Gynec. 114(1), 134-151 (1972)].

Moreover, perforation of the wall of the uterus has frequently been observed with this type of contraceptive [Buchmann, 5 Fert.Steril. 21(4), 348- 355 (1973)].

Rigidly formed intra-uterine contraceptives may break in the uterus owing to the ~~the alternating~~ bending stresses to which they are subjected. The broken pieces may be expelled spontaneously without being noticed or, as in the case of undamaged devices, 10 penetrate the wall of the uterus and enter the peritoneal cavity [Last, J.Obst. Gynec.Brit.Commonw. 79(2), 190-191 (1972); Domany et al., Brit.Med.J. 1 549 (1973)].

The use of medicament-containing intra-uterine contraceptives such as the TCu 200 or TCu 220 C, the contraceptive containing copper and zinc, or a device containing progesterone (German Patent Specification 2,247,949) or d₁-11β-ethyl-17α-ethinyl-17β-hydroxy-gon-4-en-3-one, results in an observed reduction in the pregnancy rate as compared with intra-uterine contraceptives made only of synthetic plastics material.

However, these medicament-containing intra-uterine contraceptives, like the similarly shaped devices free from medicament, lead during the period of use to undesired side effects such as haemorrhages and pains [Fortier et al., J.Amer.Obst.Gynec. 115(3), 291-297 (1973); Tatum, Contraception 6(3), 179-189 (1972); Mishell et al., Amer.J.Obst. Gynec. 116(8), 1092-1096 (1973)].

It is common to all T-shaped devices that owing to the tendency of the synthetic plastics to acquire a permanent set they cannot be sterilized in the applicator. Furthermore, it is hardly

possible to insert the device in the applicator under aseptic conditions, because the device and applicator are not fitted together in a suitable manner.

5 The device and applicator together can cause injuries during application, as the folded-up device and the upper edge of the insertion tube have sharp edges. The DALKON-Shield and the applicator developed for this device are so constituted that it is only possible to introduce the contraceptive with considerable stretching of the cervical canal.

10 In addition to the large number of enforced removals of this contraceptive owing to side effects there are also spontaneous expulsions [Fortier et al., Amer.J.Obst.Gynec. 115(3), 291-297
15 (1973); Johannisson, Contraception 8(2), 99-112 (1973); Snowden et al. Contraception 7(2), 91-104 (1973); Horowitz, Contraception 7(1), 1-10 (1973)]. Spontaneous expulsions have been observed with a few of these devices [DALKON Shield: German Offenlegungsschrift 1,956,701; Ostergard et al., Obst.Gynec. 41(2), 257-258 (1973); T-shaped contraceptives, COPPER-7: Newton et al., Lancet 1972/II No. 7784, 951-954; Bernstein et al., Contraception 6(2), 99-107 (1972)], even though they are so shaped that they have abutments so arranged as to oppose the direction of expulsion. [Jones et al., Brit.Med.J., 3, 143 (1973)]. In the DALKON Shield these abutments are fixed lateral projections in the form of fingers and prongs on a ring. Intra-uterine contraceptives so formed naturally have the risk of causing injuries to the uterus during application, during the period of use [Koetsawang, Contraception 7(4), 327-332 (1973); Johannisson, Contraception 8(2), 99-112 (1973); Lehfeldt et al., Obst. Gynecol. 37(6), 826-831 (1971); Brooks et al.,

Amer.J.Obst.Gynecol. 113(1), 104-106 (1972); Sprague et al., Obst.Gynecol. 41(1), 80-82 (1973); Rienprayura et al., Contraception 1(6), 515-521 (1973)] and during removal [Snowdon et al., Contraception 1(2), 91-104 (1973)]. KAMAL et al. [Fert.Steril. 24(3), 165-169 (1973)] describe as trivial the injuries to the wall of the uterus caused by the two horizontal ends of the T-formed contraceptive device (U.S. Patent 3,533,406), which anchor the device in the wall of the uterus, and even as being favourable to the action and fixing of the contraceptive device.

In the case of intra-uterine contraceptives containing copper, such as the COPPER-T, the copper wire may break as a result of mechanical stress or become separated from the body of synthetic plastics material. The resulting fragments of copper wire may cause injuries. They may penetrate the wall of the uterus, pass into the peritoneal cavity and, being fragments, are difficult to locate. With the COPPER-TCu 220 C the risk of perforation of the wall of the uterus with subsequent separation of the copper cylinder and the copper cylinder remaining in the peritoneal cavity is especially great.

The hitherto proposed contraceptives also have disadvantages in that their total weight or the distribution of weight within the device tend to cause spontaneous expulsion. The COPPER-TCu 220 C weighs 612 mg, and one construction of the LIPPES LOOP weighs 665 mg. Metal-containing intra-uterine contraceptives, such as that described in German Offenlegungsschrift 2,207,939, are easily expelled spontaneously (the metal rings all being fixed on the shaft of the synthetic plastics body).

Other contraceptives, for example those proposed in German Patent Specification 1,441,359 or German Offenlegungsschrift 2,207,939, have an extension of the spiral to be applied intra-uterinally, which extension extends out of the cavum uteri through the cervical canal into the vagina. These devices are made entirely of synthetic plastics material. However, the synthetic plastics suitable for forming the spiral is too rigid for the part located within the cervix and within the vagina. Therefore, with these contraceptives which extend into the cervical canal very many side effects have been observed, such as spasmodic pain and haemorrhages [WILLSON, Amer.J.Obstet.Gynecol. 92(1965)62]. The consequence of spasms of the uterus is frequently an unnoticed spontaneous expulsion and a subsequent pregnancy.

A further disadvantage of the known medicament-containing contraceptives is that the long term release of non-metallic active substances does not occur with the regularity necessary for maintaining the contraceptive action within certain predetermined limits. The large scale manufacture of contraceptives of this type is also technically difficult and necessitates the taking of many precautionary measures.

The pregnancy rate, which has been calculated by the life-table method [TIETZE, Intra-Uterine Contraception, Recommended Proc. for Data Analyses Studies in Family Planning No. 18 (Suppl.), The Population Council, New York, 1967], when the hitherto proposed intra-uterine contraceptives are used is such that they do not achieve as high a reliability in action as the known contraceptives administered per os, which contain hormones as medicinally active

substances [DAVIS, Amer.J.Obstet. Gynec. 114(1972)134; FUCHS et al., Contraception 5(1972)119].

It is an object of the present invention to make it possible to provide a universal and uncomplicated medicament-containing contraceptive for human intra-uterinal use, which is reliable in action. The contraceptive should be capable of being used without risk continuously over a period of several years without physical or psychological injury for all expected dimensions of the cavum uteri in nulliparae, nulligravidae, multiparae and multigravidae.

10 It should also be so constituted that, during its period of use, it does not check or impair subsequent fertility. The use of the medicament-containing contraceptive should not entail the risk of undesired side effects such as dysfunctional haemorrhages, infections, spasmodic pain, translocations including perforations and migrations, and the risk of spontaneous expulsions. The intra-uterine contraceptive should be so shaped, while taking into account all expected dimensions of the cavum uteri, that it cannot twist in the uterus both at high motility of the uterus and in a small cavum uteri and cannot become undesirably placed, that its position can be simply and definitely ascertained if necessary by X-rays, and is so constituted with a sufficient degree of inherent stability and the flexibility necessary for application, use and extraction having regard to the form and the material used for its manufacture, that there is substantially no risk that mechanical injury to the uterus will occur. It should be possible to introduce the contraceptive under aseptic conditions into the uterus in a simple and painless manner without appreciable dilatation of the cervical canal and without the use of further medicaments.

The applicator for the intra-uterine contraceptive should be so constituted and correlated to the device that the contraceptive can be administered under aseptic conditions.

Such medicament-containing contraceptives should be capable
5 of being manufactured and sterilized in large numbers industrially
in a simple and reliable manner. This type of contraceptive shculd,
above all, be so constituted that the probability of undesired
pregnancies during the period of use is as far as possible equal
to zero.

10 The invention provides a contraceptive consisting of round rods connecting a plurality of spheres of synthetic plastics of high elasticity, tensile strength and medium hardness having a maximum weight of 0.5 gram, and incorporating one or more pharmacologically active substances, and optionally having an intra-cervical appendage of synthetic plastics, preferably LTV-silicone elastomer, in the form of a thread or filament.

The physical properties of the synthetic plastics material may be as follows:

Modulus of elasticity (ASTM D 747 RESP.638):

20 900 to 2,900, preferably, 1,000 to 2,750, kilograms per square centimetre.

Tensile strength (ASTM D 638 RESP.412):

25 50 to 70, preferably, 60 to 105, for silicone elastomers and 150 to 550 kilograms per square centimetre for thermoplastics.

Shore hardness: A 35 to 85, preferably, 40 to 75, (DIN 53 505) for silicone elastomers, and D 40 to 70, preferably, 45 to 60 (ASTM D 676) for thermoplastics.

Several forms of intra-uterine contraceptive device constructed in accordance with the invention will now be described with reference to the accompanying drawings, in which Figures 1 and 2 are side views of two forms of device.

Referring to Fig. 1 of the accompanying drawings, the first form of device is generally Y-shaped and has a total length of 3 to 4 cm. Extending from a central sphere 1 having a diameter of 2.5 to 3.0 mm., are arranged three round rods 2 - 4 terminating in spheres and having different lengths and having diameters of 1.0 to 1.5 mm.. The rods 3 and 4 terminate at a length of 0.8 to 1.2 cm in the case of the rod 3 and 0.5 - 0.8 cm in the case of the rod 4, respectively, in spheres 5 and 6 having diameters of 4 to 5 mm. and 1.5 - 2.0 mm., respectively, and are arranged at an obtuse angle to the third rod 2. To form the stem of the Y, the third rod 2 continues into a three-rod assembly 7,8,9 connecting four spheres 10 - 13 having a diameter of 2 to 3 mm. and into a bean-like end-piece 14 having a length of 4 to 5 mm. and a diameter of 2 to 3 mm. having a central bore 15 having a diameter of 0.5 to 1.5 mm.

The angle between the axes of the rods 3 and 4 does not exceed 130 degrees and preferably does not exceed 127 degrees. Further, the angle between the axes of the rods 3 and 4 is advantageously at least 120 degrees and preferably at least 121 degrees. The angles between the axes of the rods 2 and 3 is substantially equal to the angle between the axes of the rods 2 and 4.

The eye is provided for fastening a thread 18 of suitable material, for example, nylon or polyester. This thread serves as an indicator thread for indicating in a simple manner the presence of the contraceptive device.

5 Referring to Figure 2 of the drawings, a second form of contraceptive device is similar to the first form of device except that a further thread or filament of synthetic plastics serves as an intra-cervical appendage 19 which is passed through the

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central bore 15 and secured to the end-piece 14 in addition to the indicator thread 18, and also contains one or more pharmacologically active ingredients.

This special form is shown in Fig. 2.

For making the synthetic plastics body for the contraceptive of the invention there may be used synthetic plastics, which release one or more non-metallic pharmacologically active ingredients contained in admixture or conjunction with the synthetic plastic and have adequate mechanical properties such, for example, as tensile strength, elasticity and cold stretchability, and can easily be formed into suitable shapes. As such there may be mentioned, for example, polyethylene, ethylene/vinyl acetate copolymers, ionomeric resins derived from polyethylene, polyamides, polyether-ester elastomers on a terephthalate base, polyethylene terephthalate, and also silicone rubbers. The synthetic plastics may be used singly or in combination, for example, by forming in layers. The pharmacologically active ingredients incorporated in the intra-uterine contraceptive may be metals, metal alloys or non-metallic pharmacologically active ingredients of natural or synthetic origin, which are located on the surface of the synthetic plastic body or contained in a synthetic plastics base.

As metallic active ingredients there may be mentioned, for example, metals such, for example, as copper, silver, nickel or combinations of these metals with one another and also mixtures of the pure metals with the corresponding metal alloys. The metal or metal alloys may be dispersed uniformly in the entire synthetic plastics body or only in certain parts thereof or may be applied partially and/or in alternation to the surface of the contraceptive

in a suitable manner.

The metallic pharmacologically active ingredients may be incorporated in or applied to the synthetic plastics bodies in a manner in itself known, for example, by electro-deposition, treatment with steam, reductive separation, optionally with the aid of an adhesive agent or by dispersing. In applying the metal or metals by electro-deposition the metal may separate in various forms and layers of different metals may be applied one upon another. The thickness of the layer of metal applied should be such that the metal does not become detached from the synthetic plastics body when the contraceptive is subjected in the uterus to large alternating bending stresses.

In a preferred form of the contraceptive a metallic pharmacologically active ingredient is applied to the spheres 5, 6, 10, 11, 12 and 13, and the metal on different spheres may be the same or different. The arrangement of metals on the different spheres may be in groups or alternating. Especially advantageous is an alternating arrangement of copper and nickel.

The non-metallic pharmacologically active ingredients which may be contained in contraceptives of the invention are preferably compounds having hormonal activity, local anaesthetics and weakly basic buffer substances. There may be mentioned, for example, Δ^4 -pregnen-3,20-dione (Progesterone), d-13-ethyl-17 α -ethinyl-17 β -hydroxy-4-gonen-3-one (d-norgestrel) and esters thereof, 17 α -ethinyl-19-nortestosterone (norethisterone) and esters thereof, 6-chloro-17-hydroxy-1 α ,2 α -methylene-pregna-4,6-dien-3,20-dione (cyproterone) and esters thereof, 3-methoxy-19-nor-17 α -pregna-1,3,5(10)-trien-20-yn-17-ol (mestranol), 18-methyl-19-nor- Δ^4 -pregnen-17 α -ol-3,20-

dione-17 α -caproate, 3-hydroxy-1,3,5(10)-oestratrien-17-one (oestrone),
17-acetoxy-6 β ,7 β -epoxy-1 α ,2 α -methylene-4-pregn-3,20-dione,
4,6-dichloro-17-acetoxy-16 α -methyl-4,6-pregnadien-3,20-dione,
17 α -hydroxy-6-methyl-pregna-4,6-dien-3,20-dione acetate (megestrol
5 acetate), 19-nor-5 α -pregnan-3,20-dione, 3 β -hydroxy-19-nor-5 α -
pregnan-20-one, 19-norhydroxyprogesterone and esters thereof,
6-chloro-17-hydroxy-pregna-4,6-dien-3,20-dione acetate (chlormadinone
acetate), 1,3,5(10)-oestratrien-3,17 β -diol (oestradiol), 1,3,5(10)-
oestratrien-3,16 α ,17 β -triol (oestriol), 17 β -hydroxy-4-androsten-3-
10 one (testosterone) and esters thereof, 21-hydroxy-5 β -pregnan-3,20-
dione and esters thereof, 17 α -acetoxy-6 α -methyl-progesterone
(medroxy-progesterone acetate), 10 α -pregna-4,6-dien-3,20-dione
(dydrogesterone), 17 β -oestradiol, and xylocaine, novocaine,
triethanolamine, disodium ethylene diamine tetracetate and phosphate
buffers of Sörensen.

The non-metallic pharmacologically active ingredients may
be in admixture or conjunction with the synthetic plastics body.
For example, they may be dispersed homogeneously in the synthetic
plastics body, if desired with the use of auxiliary substances,
or contained in separate parts of the contraceptive device in
suitable quantities with or without these auxiliary substances,
for example, as a core member in a part of the synthetic plastics
body. Such auxiliary substances may be, for example, tenside,
highly dispersed silicon dioxide, anti-foaming agents, solubilisers,
resorption retarders, X-ray contrast agents, and ferro-magnetic
substances for assisting in ascertaining the location of the
contraceptive device .

A preferred form of the contraceptive contains d-13-ethyl-

1.7 α -ethinyl-17 β -hydroxy-4-gonen-3-one (d-norgestrel) homogeneously dispersed in a silicone rubber base that vulcanises at a slightly raised temperature, contains 5% by weight of barium sulphate and is strengthened with highly dispersed silicon dioxide.

5 A further form of the contraceptive of the invention contains in the spheres 5, 6, 10, 11, 12 and 13 core members that consist of a mixture of 6-chloro-17-hydroxy-1 α ,2 α -methylene-pregna-4,6-dien-3,20-dione acetate (cyproterone acetate) and lactose, the synthetic plastics body of this contraceptive consisting of an 10 ethylene/vinyl acetate copolymer. The core members may have a cylindrical surface and end faces of which the radius of curvature is within the range of from the radius of the cylindrical surface (giving substantially spherical core members) to infinity (giving cylindrical core members).

15 The pharmacologically active ingredients contained in the thread-shaped appendage 19 are arranged to be released in a controlled manner from the carrier material of synthetic plastics at a given level within certain predetermined limits over a limited period, that is to say, in the first months of use of the contraceptive, 20 and subsequently the contraceptive action is derived from the contraceptive device, which, containing an active ingredient is also active on its own.

25 The appendage 19 can also be used with other contraceptive devices capable of intra-uterine use, which are suitable according to known practice for connection, for example, by knotting, adhesion or welding, to an intra-cervical thread-shaped medicament carrier. There may be mentioned more especially contraceptives

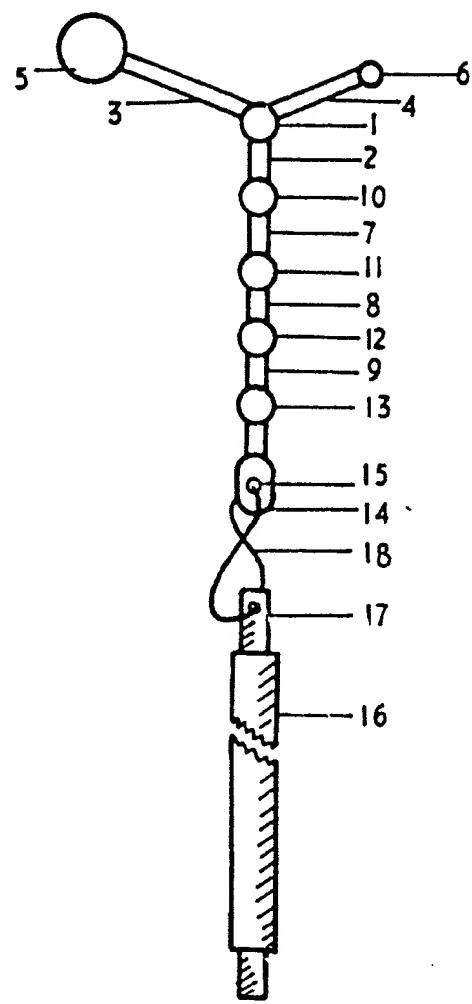


FIGURE . 1 .

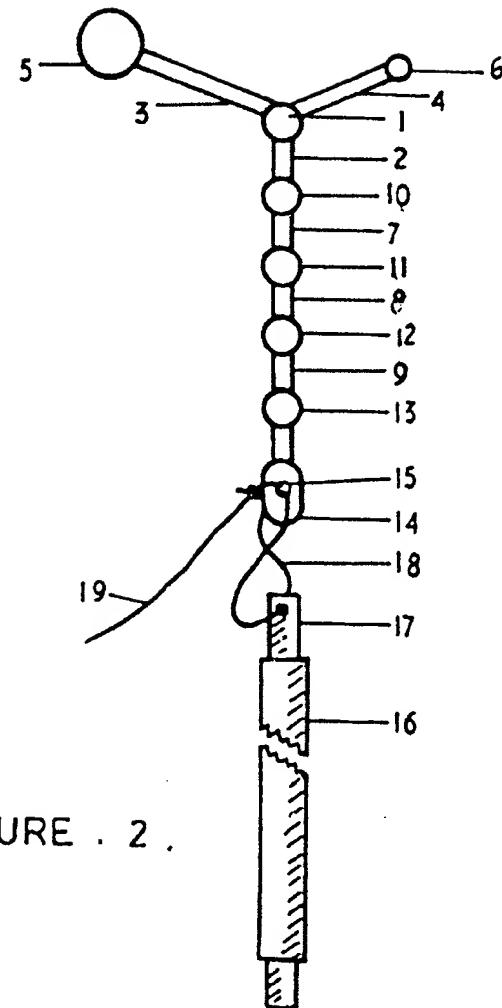


FIGURE . 2 .